Similar cerebral protective effectiveness of antegrade and retrograde cerebral perfusion combined with deep hypothermia circulatory arrest in aortic arch surgery: A meta-analysis and systematic review of 5060 patients

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Objective: Our objective was to determine if antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP) combined with deep hypothermia circulatory arrest in aortic arch surgery results in different mortality and neurologic outcomes.

Methods: The Cochrane Library, Medline, EMBASE, CINAHL, Web of Science, and the Chinese Biomedical Database were searched for studies reporting on postoperative strokes, permanent neurologic dysfunction, temporary neurologic dysfunction, and all causes mortality within 30 days postoperation in aortic arch surgery. Meta-analysis for effect size, *t* test, and I^2 for detecting heterogeneity and sensitivity analysis for assessing the relative influence of each study was performed.

Results: Fifteen included studies encompassed a total of 5060 patients of whom 2855 were treated with deep hypothermic circulatory arrest plus ACP and 1897 were treated with deep hypothermic circulatory arrest plus RCP. Pooled analysis showed no significant statistical difference ($P > .01$) of 30-day mortality, permanent neurologic dysfunction, and transient neurologic dysfunction in the 2 groups. Before sensitivity analysis, postoperative stroke incidence in the ACP group was higher than in the RCP group (7.2% vs 4.7%; $P < .01$). After a study that included a different percentage of patients with a history of central neurologic events in the 2 groups was ruled out, postoperative stroke incidence in the 2 groups also showed no significant statistical difference ($P > .01$).

Conclusions: ACP and RCP provide similar cerebral protective effectiveness combined with deep hypothermia circulatory arrest and could be selected according to the actual condition in aortic arch surgery. A high-quality randomized controlled trial is urgently needed to confirm this conclusion, especially for stroke morbidity following ACP or RCP. (J Thorac Cardiovasc Surg 2014;148:544-60)

Despite the progress made in the past decades in aortic arch surgery, this kind of procedure is associated with a high rate of mortality and morbidity.[1] This is not due to the technical difficulties of the procedure, but mainly to the necessity of protecting the integrity of the central nervous system during the period of arch exclusion.[2]

Deep hypothermic circulatory arrest (DHCA) has been used in aortic arch surgery as an effective cerebral protective technique for more than 3 decades and has been refined by Griepp and colleagues.[3,4] Although hypothermia has proven to be a feasible means of protection of any organ, a time-dependent cascade of events resulting in brain cell injury is initiated. Concerns about the increased mortality and risk of neurologic deficit led to implementation of adjuncts, such as antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP), which might enhance the safety of the DHCA technique.[5]

Both ACP and RCP have their own advantages and disadvantages. ACP can provide independent control of temperature and/or flow to the cerebral and systemic circulation, but has the potential for embolization. RCP can flush potential embolus from the cerebral circulation and it avoids manipulation of the arch vessel, but the cerebral perfusion capability of RCP is unclear.[6,7] Furthermore, venous valves may compromise blood flow and RCP may result in cerebral edema.[8]

Unfortunately, a high-quality, multicentric, randomized controlled trial comparing the effectiveness of ACP and

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Abbreviations and Acronyms

ACP = antegrade cerebral perfusion
DHCA = deep hypothermic circulatory arrest
PND = permanent neurologic dysfunction
RCP = retrograde cerebral perfusion
TND = transient neurologic dysfunction

RCP combined with DHCA in preventing neurologic deficit is absent, making it difficult to draw any meaningful conclusions as to which treatment option is better. The aim of our study was to assess the risk of neurologic complications by meta-analysis of published trials comparing ACP and RCP combined with DHCA.

METHODS

We searched the Cochrane Central Register of Controlled Trials in the Cochrane Library, Medline, EMBASE, CINAHL, Web of Science, and the Chinese Biomedicine Database for studies until April 26, 2013. The following free text search string was used: "human and antegrade cerebral perfusion or retrograde cerebral perfusion or selective cerebral perfusion or antegrade brain perfusion or ACP or ASCP or RCP or cerebral protection or hypothermia circulatory arrest or HCA or DHCA and comparative study or randomized controlled trial."

Studies that evaluated the cerebral protective effectiveness of ACP and RCP combined with DHCA were included. We looked for studies that gave at least 1 of the following clinical outcomes: all-cause mortality within 30 days, morbidity of transient neurologic dysfunction (TND) (defined as postoperative confusion, agitation, delirium, prolonged obtundation, or transient parkinsonism), permanent neurologic dysfunction (PND) (ie, presence of permanent neurologic deficits that were focal or global in nature and persisting at discharge from the hospital), and stroke (defined as a serious illness caused when a blood vessel in the brain suddenly breaks or is blocked, diagnosed by computed tomography or magnetic resonance imaging).[9]

Two authors (Drs Zhipeng and Hongbing) independently identified trials for inclusion and extracted information on demographics, interventions, and outcomes. Disagreements were resolved by consensus. For dichotomous and continuous variables, risk ratios (RRs), 95% confidence intervals (CIs), and odds ratios (ORs) were calculated. And for continuous variables, mean difference and 95% CIs were calculated. Statistical heterogeneity was measured using the Q statistic and I^2 test ($Q < 0.10$ or $I^2 > 50\%$ was considered an indication of statistically significant heterogeneity). For each outcome, the fixed effect model (Mantel-Haenszel test for dichotomous variables and inverse variance for continuous variables) or random effects model (DerSimonian and Laird method for dichotomous and continuous variables) was used when the Q statistic suggested lack or presence of heterogeneity, respectively. The sensitivity analyses were used to assess the relative influence of each study on pooled estimates by omitting 1 study at a time. Finally, we assessed the publication bias by using funnel plots. All analyses were done with Stata software (version 12, StataCorp LP, College Station, Tex).

RESULTS

Included Studies

Of 1843 potentially relevant studies, 15 comparative studies met the selection criteria and were included[10-24] (Figure 1). No randomized controlled trial is available. The included studies encompassed a total of 5060 patients

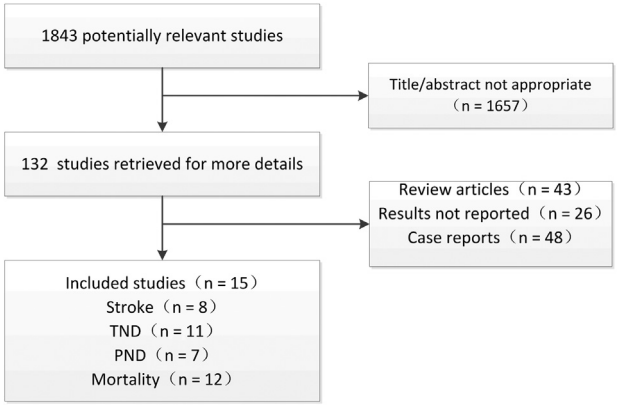

FIGURE 1. Flow diagram of study selection. *TND,* Transient neurologic dysfunction; *PND,* permanent neurologic dysfunction.

of whom 3156 were treated with DHCA + ACP and 1904 were treated with DHCA + RCP. Baseline patient characteristics and main intraoperative details are shown in Table 1. A significant difference only exists in the comparison of the central neurologic event's history before surgery between the 2 groups ($P < .01$). Unfortunately, some important information about proportions of acute and/or chronic dissections, of redo procedures, the extent of the aortic replacement, and the type of cannulation were only presented by part of the studies and could not be compared. Quality assessment of each comparison was done by the GRADE system and the quality of each comparison is only from very low to low (Table 2).[25-27] That may be due to the low quality of the original studies (Figure 2).

Neurologic Complications

Stroke. Postoperative strokes were observed in 8 trials comprising a total of 222 events among 3429 patients. Meta-analysis of these studies using a fixed-effects model ($P = .40$; $I^2 = 3.9\%$) revealed that ACP accounts for higher morbidity of stroke. (Mantel-Haenszel fixed RR, 1.86; 95% CI, 1.30-2.65; $P = .001$) (Figure 3). A funnel plot showed significant publication bias existed (Figure 4).

TND. Postoperative TND was observed in 11 trials comprising a total of 316 events among 4417 patients. The incidence of postoperative TND was 7.50% in the ACP group and 8.7% in the RCP group. No significant difference existed (Mantel-Haenszel fixed RR, 0.89; 95% CI, 0.72-1.1; $P = .275$). There was no heterogeneity between the 2 groups ($P = .154$; $I^2 = 29.8\%$) (Figure 5). The funnel plot showed no evidence of publication bias (Figure 6).

PND. Postoperative PND was reported in 2904 ACP patients and 1583 RCP patients from 7 studies. There was no evidence of heterogeneity ($P = .525$; $I^2 = 0\%$). Difference in postoperative PND incidence was not significant between the 2 groups (6% vs 4.7%, Mantel-Haenszel fixed RR, 1.02; 95% CI, 0.75-1.37; $P = .911$) (Figure 7). The funnel plot showed no evidence of publication bias (Figure 8).

TABLE 1. Baseline data for this study

Study	Methods	n	Age, y	Men	HCNE	PCS	Dissec-tion	Aneurysm	DHCA time	CPB time	Core temperature	Circulatory arrest time	CP time	Arch replacement type	
														Hemi	Total
Okita 2001	ACP	30	67.6 ± 8.5	25	0	NA	27	3	54.5 ± 26.2	215 ± 83	22.1 ± 3.0	NA	117 ± 40.3	NA	NA
	RCP	30	69.1 ± 10.	24	2	NA	25	5	44.3 ± 13.9	175 ± 58	17.6 ± 2.4	44.3 ± 13.9	33.1 ± 11.4	NA	NA
Matalanis 2003	ACP	25	66.5 ± 12.85	21	6	6	4	1	11.4 ± 9.6	247.8 ± 86.4	~19	61.8 ± 44.1	49.6 ± 0.5	19	6
	RCP	23	62.7 ± 11.1	16	2	4	9	17	37.4 ± 19.2	193.5 ± 34.9	~19	36.4 ± 20.5	30.6 ± 19.0	17	6
Neri 2004	ACP	25	59.9 ± 7.6	17	NA	NA	7	5	NA	164 ± 32.2	20.9 ± 1.7	NA	NA	15	10
	RCP	19	69.9 ± 3.8	14	NA	NA	18	14	NA	172.4 ± 47.9	20.9 ± 1.1	NA	NA	10	9
Zierer 2005	ACP	38	62 ± 11	28	3	2	NA	1	NA	120 ± 50	21 ± 1.3	NA	23 ± 9	NA	NA
	RCP	18	55 ± 11	9	1	0	NA	1	NA	176 ± 34	20.8 ± 2.4	NA	29 ± 13	NA	NA
Han 2007	ACP	35	NA	NA	NA	NA	14	21	51.3 ± 19	181.1 ± 73	16 ± 22	NA	NA	24	6
	RCP	43	NA	NA	NA	NA	19	24	46.6 ± 17.1	168.7 ± 59.5	16 ± 22	NA	NA	29	8
Apostolakis 2008	ACP	23	61 ± 15.6	16	2	NA	33	NA	39 ± 13.16	179 ± 28.65	16 ± 20	39 ± 13.16	37 ± 14	13	10
	RCP	25	60 ± 17.1	20	1	NA	25	NA	36 ± 12.73	184 ± 33.12	16 ± 20	36 ± 12.73	34 ± 12	17	5
Sundt 2008	ACP	74	64 ± 16	36	8	26	25	39	41 ± 28	188 ± 62	NT 16-18	41 ± 28	NA	24	82
	RCP	53	71 ± 8	27	2	12	18	28	33 ± 13	176 ± 65	NT 16-18	33 ± 13	NA	32	26
Apaydin 2009	ACP	19	60 ± 13	NA	NA	NA	NA	NA	28 ± 12	251 ± 66	~16	28 ± 12	73 ± 26	NA	NA
	RCP	94	54 ± 12	NA	NA	NA	NA	4	40 ± 11	183 ± 41	~16	40 ± 11	40 ± 11	NA	NA
Forteza 2009	ACP	26	NA	NA	NA	NA	NA	4	NA	NA	~18	NA	NA	NA	NA
	RCP	23	NA	NA	NA	NA	NA	NA	NA	NA	~18	NA	NA	NA	NA
Milewski 2010	ACP	94	64.1 ± 11.5	60	13	20	5	89	34.5 ± 8.1	171.2 ± 50.3	NA	34.5 ± 8.1	30.7 ± 7.5	NA	NA
	RCP	682	59.9 ± 15.3	467	80	168	68	637	25.0 ± 9.7	222.9 ± 63.7	NA	25 ± 9.7	25 ± 9.7	NA	NA
Sugiura 2012	ACP	94	67.2 ± 9.3	45	NA	NA	NA	NA	65 ± 15	229 ± 72	25.6 ± 1.2	NA	NA	NA	NA
	RCP	109	65.6 ± 11.7	53	NA	NA	NA	NA	53 ± 16	211 ± 51	23.7 ± 1.1	NA	NA	NA	NA
Wiedemann 2012	ACP	91	62 (33-85)	63	3	5	NA	NA	47 (18-150)	161 (101-303)	ET 18	30 (14-92)	NA	NA	4
	RCP	122	56 (18-87)	75	9	7	NA	NA	63 (30-162)	198 (121-404)	ET 18	30 (14-88)	NA	NA	3
Usui 2012	ACP	2209	70.4 ± 9.9	642	342	146	NA	NA	NA	NA	NA	NA	NA	NA	NA
	RCP	583	66.9 ± 11.4	393	64	49	NA	NA	NA	NA	NA	NA	NA	NA	NA
Misfeld 2012	ACP	365	63 ± 13	234	23	51	149	27	23.7 ± 19.7	210 ± 76	22 ± 2	18 ± 12	NA	42	238
	RCP	51	62 ± 14	38	5	12	14	216	18 ± 12	205 ± 60	22 ± 2	23 ± 20	NA	9	137
Williams 2012	ACP	8	61.5 ± 11.7	5	2	0	NA	NA	34 ± 11	190 ± 43	17 ± 4.1	NA	NA	7	1
	RCP	29	59.2 ± 13.7	20	0	2	NA	NA	33 ± 11	188 ± 58	19 ± 2.7	NA	NA	28	1
P for ACP vs RCP			.68	.17	<.01	0.18	NC	NC	.56	.47	NC	NC	NC	NC	NC

Data are presented as number, median (range), or number (%). Times are given in minutes and temperatures are given in °C. *HCNE*, History of central neurologic events; *PCS,* previous cardiovascular surgery; *DHCA*, deep hypothermic circulatory arrest; *CPB*, cardiopulmonary bypass; *CP*, cerebral perfusion; *ACP*, antegrade cerebral perfusion; *NA*, not applicable; *RCP*, retrograde cerebral perfusion; *NT*, nasopharynx temperature; *ET*, esophageal temperature; *NC*, not comparable because too much data not available.

TABLE 2. Quality assessment of each comparison, describing in detail the principal findings of this review and the quality of the evidence for each outcome using the GRADE approach[25-27]

Quality assessment						No. of patients			Effect			
Studies (No.)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outcome	Control	RR (95% CI)	Absolute	Quality	Importance
Stroke (8)	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	178/2485 (7.2%)	44/944 (4.7%) 5.8%	1.86 (1.30-2.65)	40 more per 1000 (from 15 more to 75 more) 49 more per 1000 (from 18 more to 90 more)	⊕⊕OOLOW	Very important
TND (11)	Observational studies	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None	227/3039 (7.5%)	156/1794 (8.7%) 15.2%	0.89 (0.72-1.11)	10 fewer per 1000 (from 27 fewer to 9 more) 17 fewer per 1000 (from 45 fewer to 15 more)	⊕OOOVERY LOW	Very important
PND (7)	Observational studies	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	Reporting bias	173/2904 (6%)	74/1583 (4.7%) 4.3%	1.02 (0.75-1.37)	1 more per 1000 (from 12 fewer to 18 more) 1 more per 1000 (from 11 fewer to 17 more)	⊕OOOVERY LOW	Very important
Mortality (12)	Observational studies	No serious risk of bias	Serious	No serious indirectness	No serious imprecision	None	159/3067 (5.2%)	90/1739 (5.2%) 8.3%	1.12 (0.84-1.49)	6 more per 1000 (from 8 fewer to 26 more) 10 more per 1000 (from 13 fewer to 40 more)	⊕OOOVERY LOW	Very important

RR, Relative risk; *CI,* confidence interval; *TND,* transient neurologic dysfunction; *PND,* permanent neurologic dysfunction; *No.*, the number of studies on this topic.

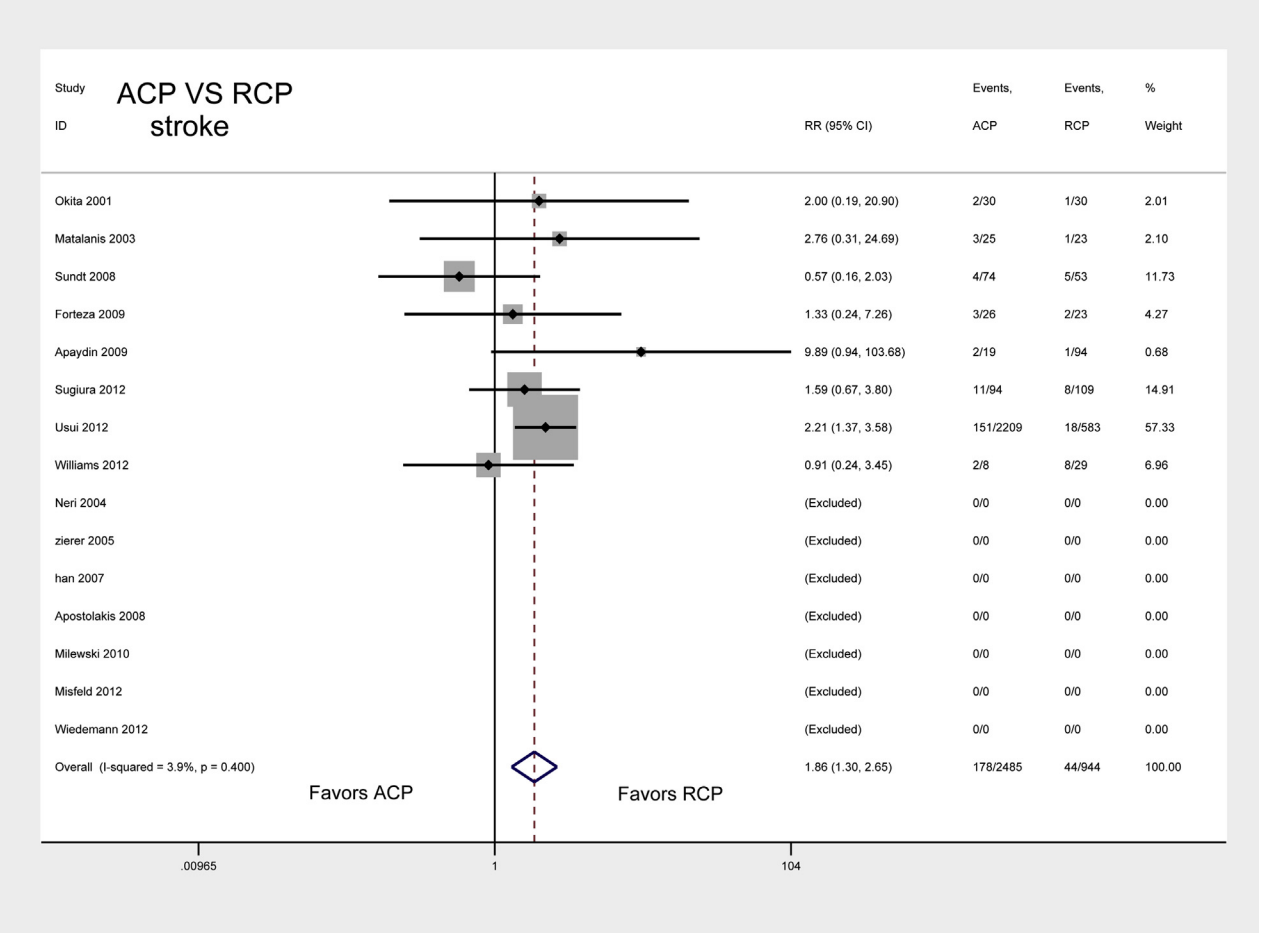

FIGURE 2. Quality assessment of each original study. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *RR*, relative risk; *CI*, confidence interval.

Mortality

All-cause deaths within 30 days were observed in 12 studies comprising a total of 249 events among 4806 patients. The incidence of postoperative mortality was 5.184% in the ACP group and 5.175% in the RCP group. No significant difference existed (Mantel-Haenszel fixed RR, 1.12; 95% CI, 0.84-1.49; $P = .432$); There was no heterogeneity between the 2 groups ($P = .175$; $I^2 = 27.5\%$) (Figure 9). The funnel plots showed significant publication bias existed (Figure 10).

Sensitivity Analysis

In the sensitivity analysis, the exclusion of any individual studies did not modify estimates of TND, PND, and mortality. But when the study by Usui and colleagues[20] was excluded, the estimate of stroke morbidity modified significantly (Figures 11 and 12) (RR, 1.86; 95% CI, 1.30-2.65 vs RR, 1.38; 95% CI, 0.83-2.32). The significant statistical difference indicated by a P value also disappeared. This indicates that the higher stroke morbidity may come from the patients in the study by Usui and colleagues.[20]

To further rule out the possibility that stroke morbidity is different in ACP and RCP groups, a sensitivity analysis was conducted on the baseline data. When the study by Usui and colleagues[20] was excluded, the significant statistical difference in central neurologic events history also disappeared, and the estimate of stroke morbidity modified significantly (Figure 13) (RR, 1.33; 95% CI, 1.08-1.64 vs RR, 1.15; 95% CI, 0.80-1.66) (Figures 14 and 15). This indicates a higher rate of central neurologic events history before surgery in the patients included in the study by Usui and colleagues.[20] The higher incidence of stroke may come from including more patients with a history of central neurologic events in the ACP group but not from the ACP procedure.

DISCUSSION

DHCA was the first method of brain protection successfully used in aortic arch surgery but has temporal limits. Both ACP and RCP have additional brain protective effects, but along with those are potential risks. Theoretically, ACP may present higher risk of cerebral embolism, whereas RCP

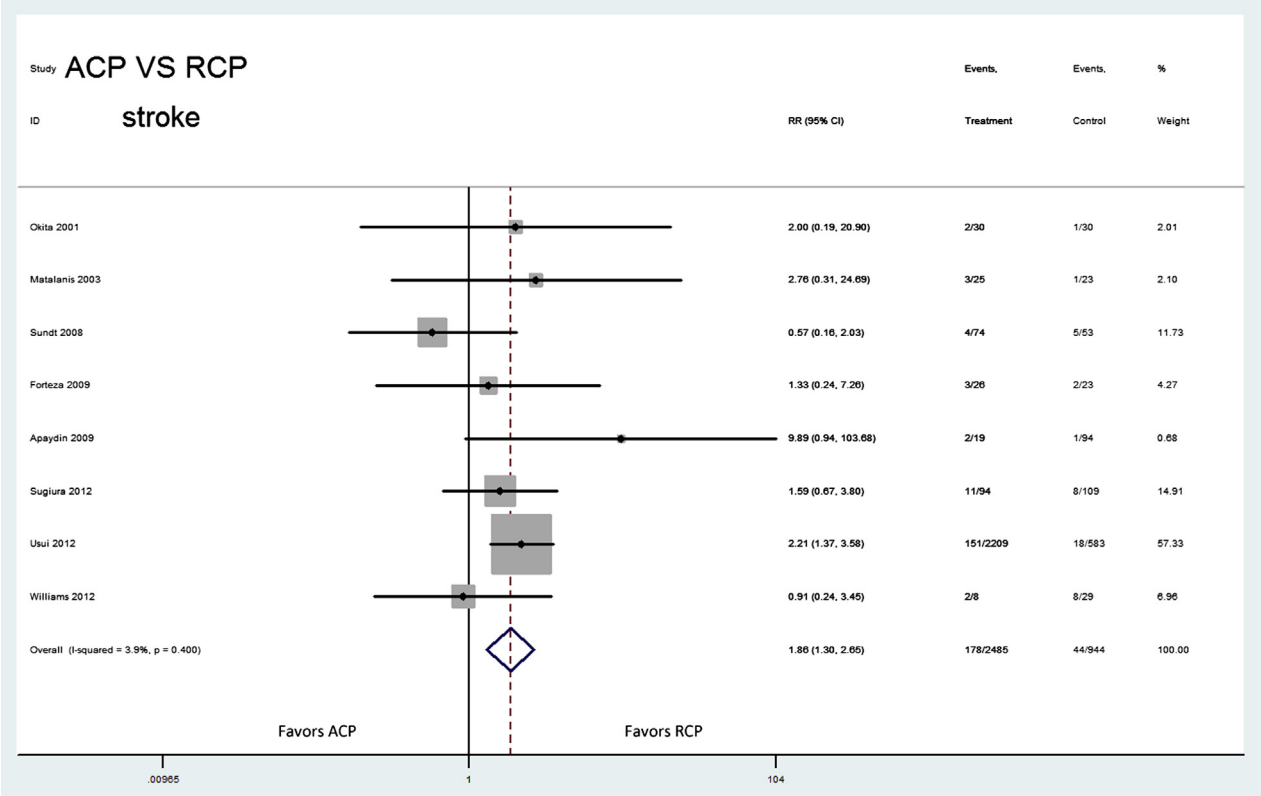

FIGURE 3. Comparison of antegrade cerebral perfusion (*ACP*) versus retrograde cerebral perfusion (*RCP*) for morbidity of postoperative stroke. *RR,* Relative risk; *CI,* confidence interval.

may present higher risk of cerebral hypoperfusion.[8] No consensus has been reached on which procedure—ACP or RCP—gives better clinical brain protection effectiveness. The main finding of our study is that no difference exists between ACP and RCP in regard to protecting the central cerebral system during aortic arch surgery.

Although Usui and colleagues[20] drew a conclusion by risk-adjusted analysis that both RCP and ACP provide comparable clinical outcomes regarding stroke rates, when their data was entered into our meta-analysis, both central neurologic events history before surgery as baseline data and stroke incidence as a result are significantly different between the ACP and RCP groups. Fortunately, we successfully ruled out such a special patient group with a discrepant baseline with the help of the strong sensitivity analysis function of Stata software and drew an absolute opposite conclusion, which means, based on similar baseline data, that ACP and RCP account for the same postoperative stroke rates. Previous investigators also identified history of central neurologic events as a predictor of postoperative stroke.[28,29] Those studies provide further support to our finding.

When compared with other clinical neurologic outcomes, such as TND, PND, and all-cause deaths within 30 days, ACP and RCP provide similar protection effectiveness. Several studies have reported that PND is more likely to occur after ACP because of embolism and TND was more likely to occur after RCP because of global ischemia and a longer cerebral ischemic time.[29-32] In our meta-analysis, there was no difference in TND and PND between the RCP group and the ACP group, suggesting that both techniques provide acceptable cerebral outcomes. The technique best suited to the individual patient can therefore be selected.

This meta-analysis focused on the influence of cerebral protective method selected on the main neurologic complications that result. Other clinical results such as respiratory failure, renal failure, hepatic injury, and cardiovascular accident were not compared. This is partially because of the dominant incidence of neurologic complications after arch surgery and their bad prognosis. So our conclusion is most valuable when used as a resource to select a better cerebral scheme when the prevention of neurologic complications is most important.

Because ACP and RCP worked equally well with DHCA, it seems that hypothermia was the key ingredient and the perfusion was nonessential. In fact, our meta-analysis could have been designed to compare DHCA alone, DHCA + ACP, or DHCA + RCP. But only a few studies compared results from these 3 methods and there are not

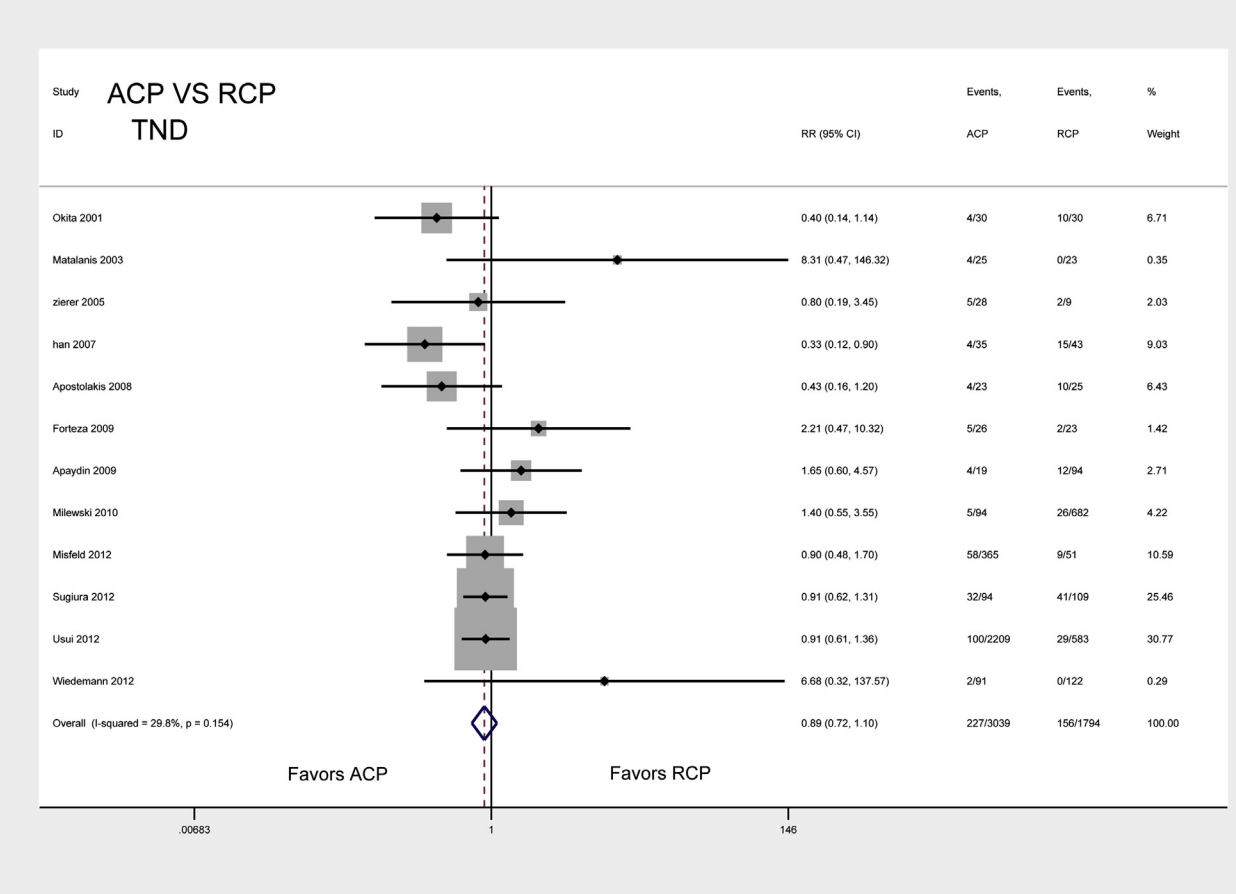

FIGURE 4. Funnel plot of comparison: Morbidity of postoperative stroke. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *TND*, transient neurologic dysfunction; *RR*, relative risk; *CI*, confidence interval.

enough data for a meta-analysis. But most of these studies reached the same conclusion that DHCA + ACP or RCP are better than DHCA alone, especially when the requiring brain protection time is longer than 30 minutes.[10,14,16,29,33]

We assessed the quality of the original studies by the GRADE system. Although the quality of each study is not so high and the level of evidence provided by the studies is weak, the conclusion of this meta-analysis is still valuable—especially before a high-quality RCT is published.

There are limitations to this meta-analysis. First, no randomized controlled trial is available and the quality of each study included is low, so a high-quality meta-analysis of randomized controlled trials could not be performed. Second, some of the important baseline data are not available, such as hypertension and peripheral vascular disease. This prevented us from comparing clinical outcomes of ACP and RCP based on more similar baseline data.

CONCLUSIONS

ACP and RCP provide similar cerebral protective effectiveness when combined with DHCA and could be selected according to the actual condition in aortic arch surgery. A high-quality randomized controlled trial is urgently needed to confirm this conclusion, especially for stroke morbidity following ACP or RCP.

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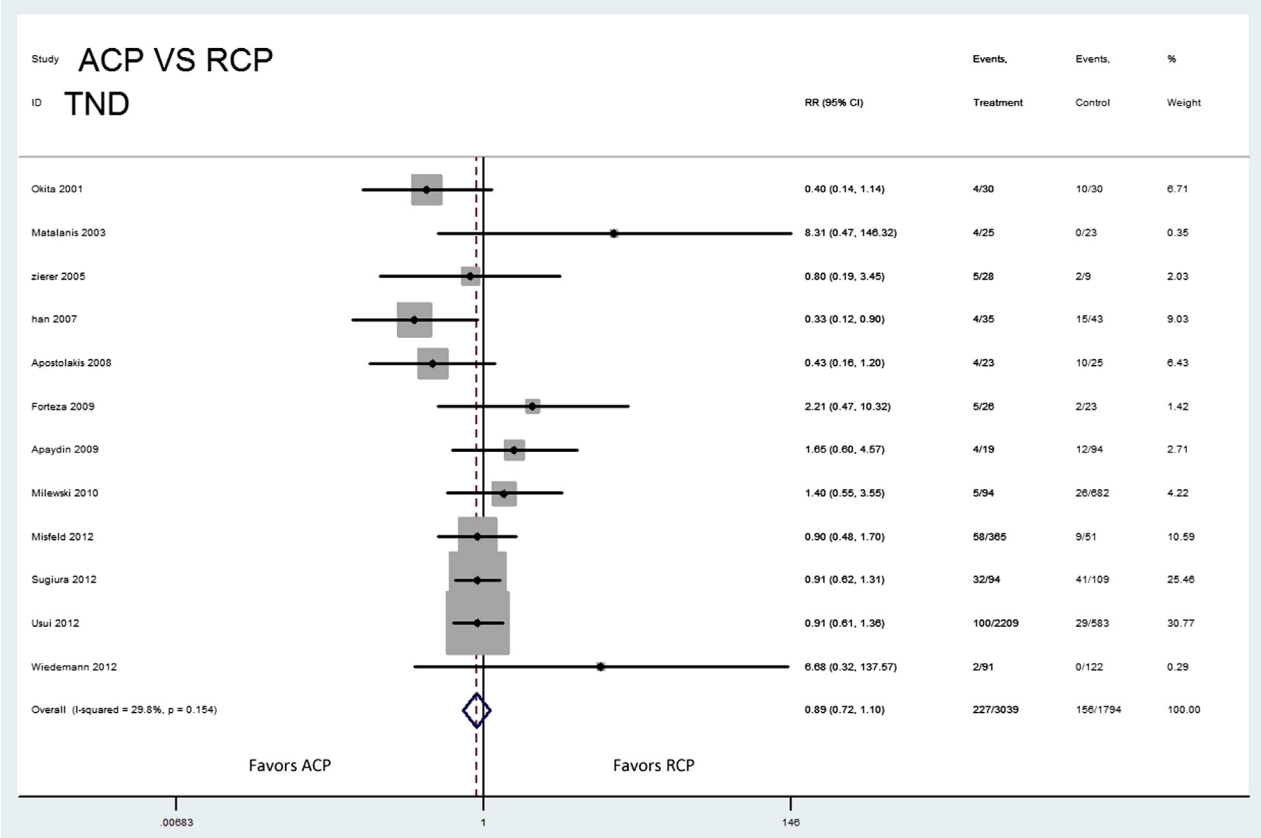

FIGURE 5. Comparison of antegrade cerebral perfusion (*ACP*) versus retrograde cerebral perfusion (*RCP*) for morbidity of postoperative transient neurologic dysfunction (*TND*). *RR,* Relative risk; *CI,* confidence interval.

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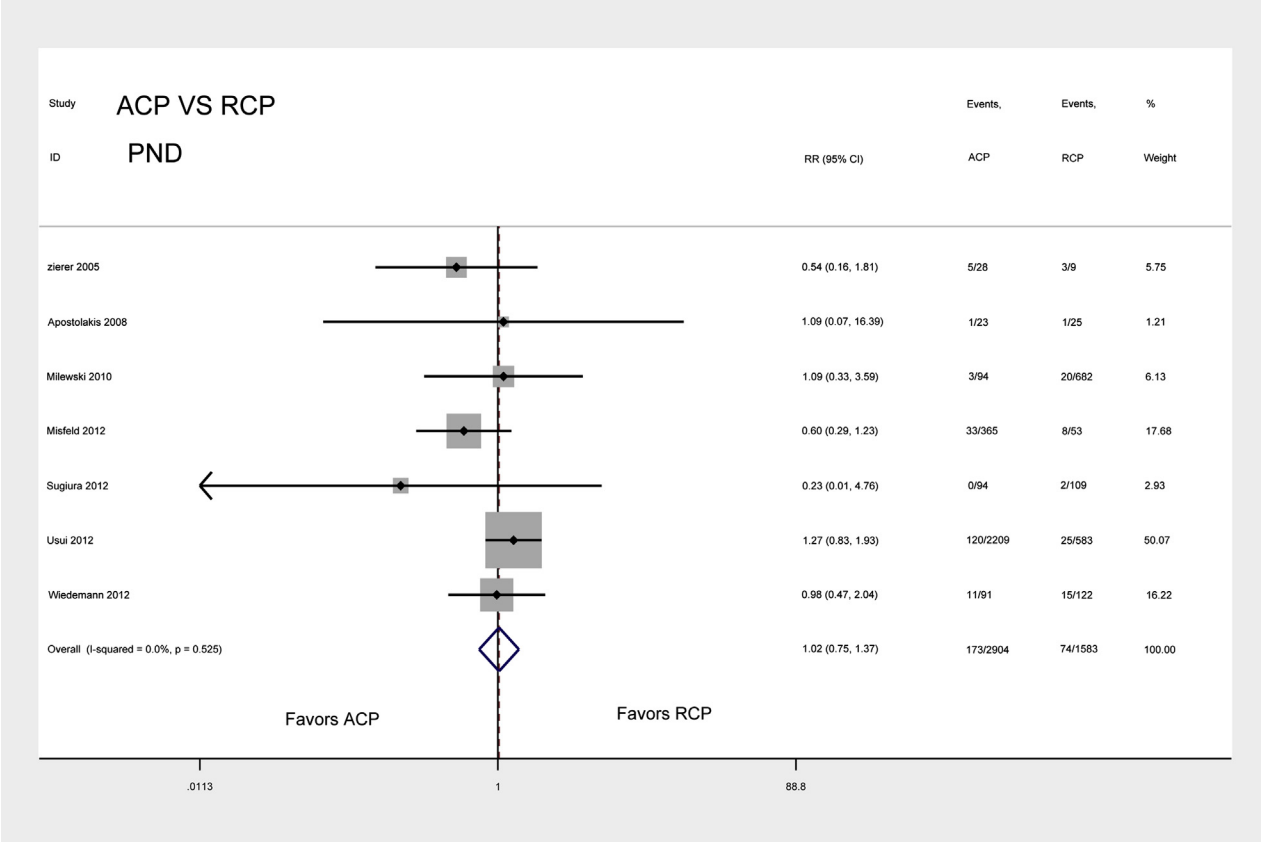

FIGURE 6. Funnel plot of comparison: Morbidity of postoperative transient neurologic dysfunction. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *PND*, permanent neurologic dysfunction; *RR*, relative risk; *CI*, confidence interval.

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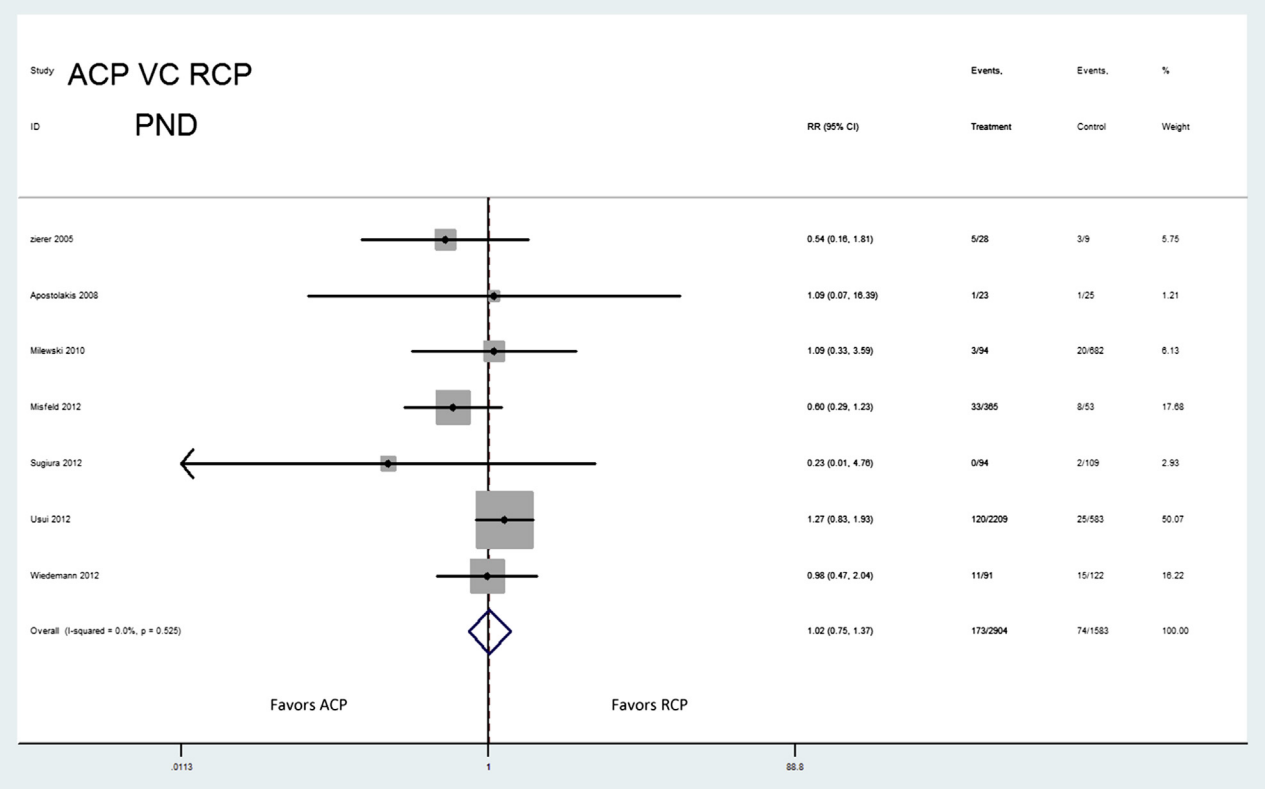

FIGURE 7. Comparison of antegrade cerebral perfusion (*ACP*) versus retrograde cerebral perfusion (*RCP*) for morbidity of postoperative permanent neurologic dysfunction (*PND*). *RR,* Relative risk; *CI,* confidence interval.

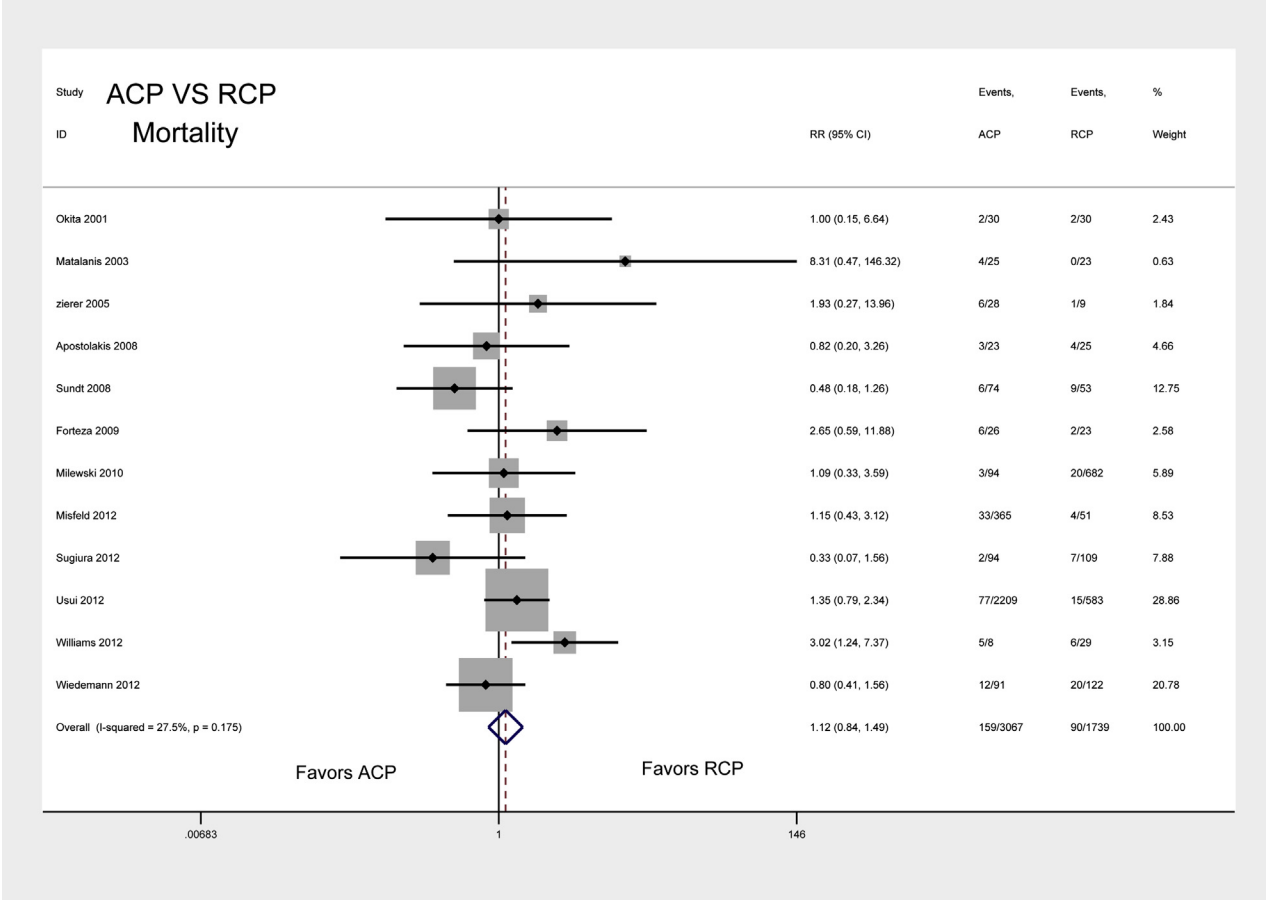

FIGURE 8. Funnel plot of comparison: Morbidity of postoperative permanent neurologic dysfunction. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *RR*, relative risk; *CI*, confidence interval.

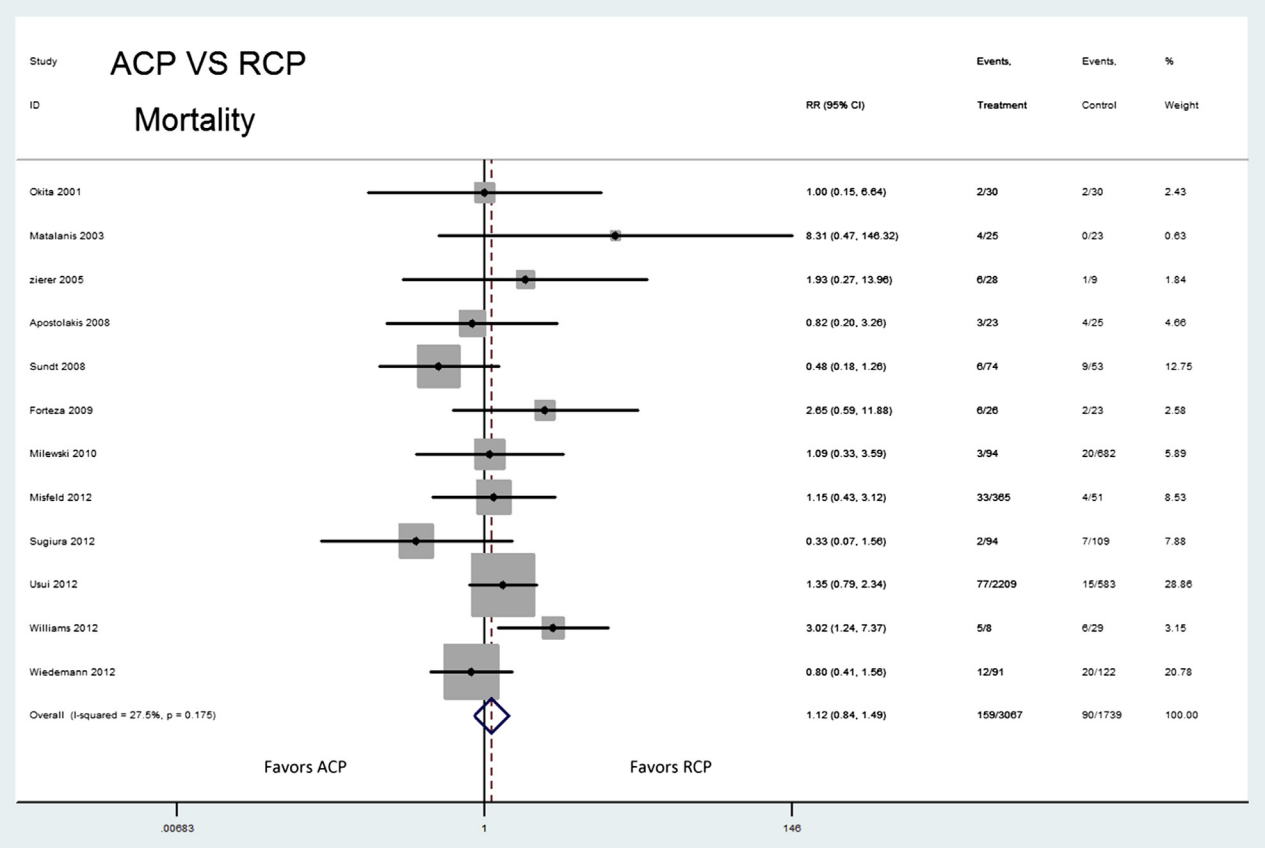

FIGURE 9. Comparison of antegrade cerebral perfusion (*ACP*) versus retrograde cerebral perfusion (*RCP*) for postoperative in-hospital mortality. *RR,* Relative risk; *CI,* confidence interval.

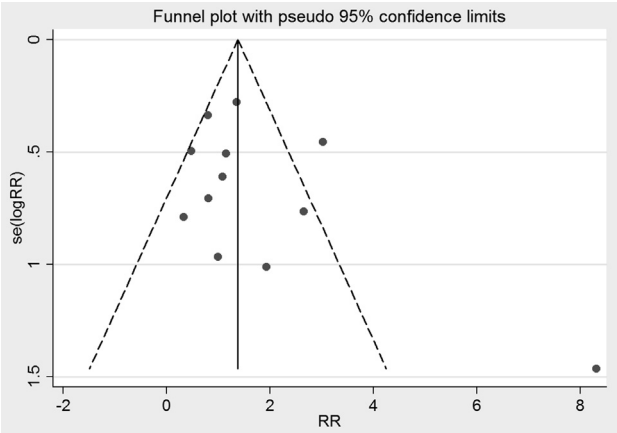

FIGURE 10. Funnel plot of comparison: Postoperative in-hospital mortality. *se,* Standard error; *RR,* relative risk.

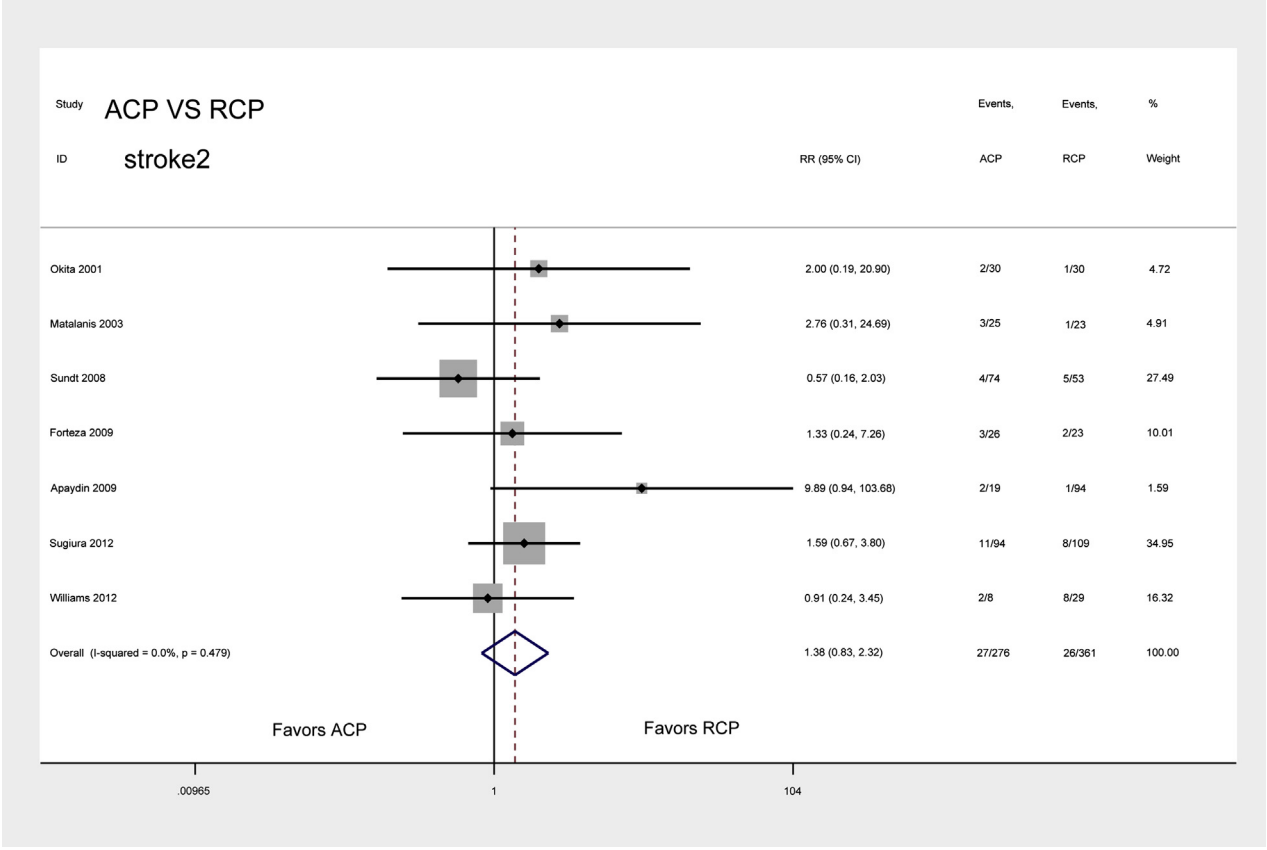

FIGURE 11. Sensitivity analysis of stroke indicating that exclusion of the study by Usui and colleagues[20] changes the total results most obviously. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *RR*, relative risk; *CI*, confidence interval.

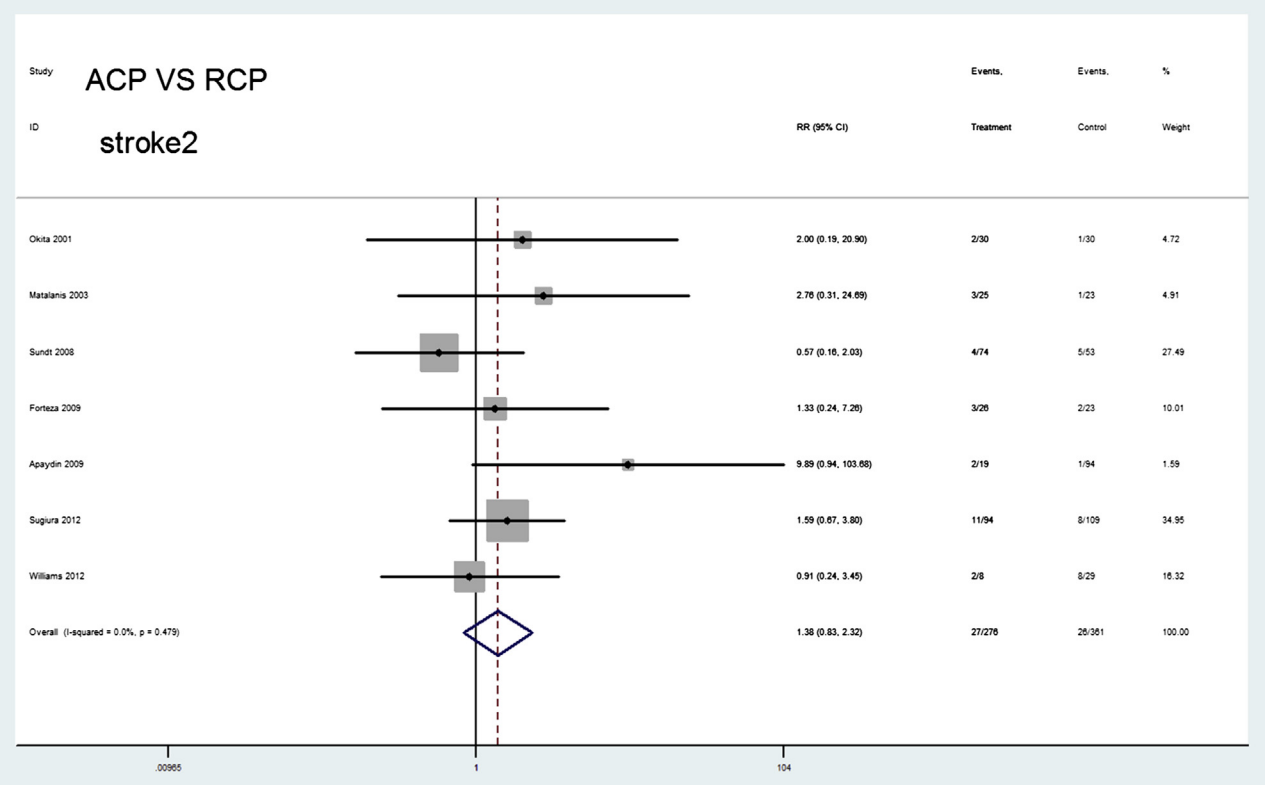

FIGURE 12. Comparison of antegrade cerebral perfusion (*ACP*) versus retrograde cerebral perfusion (*RCP*) for morbidity of postoperative stroke after study by Usui and colleagues[20] was excluded. *RR,* Relative risk; *CI,* confidence interval.

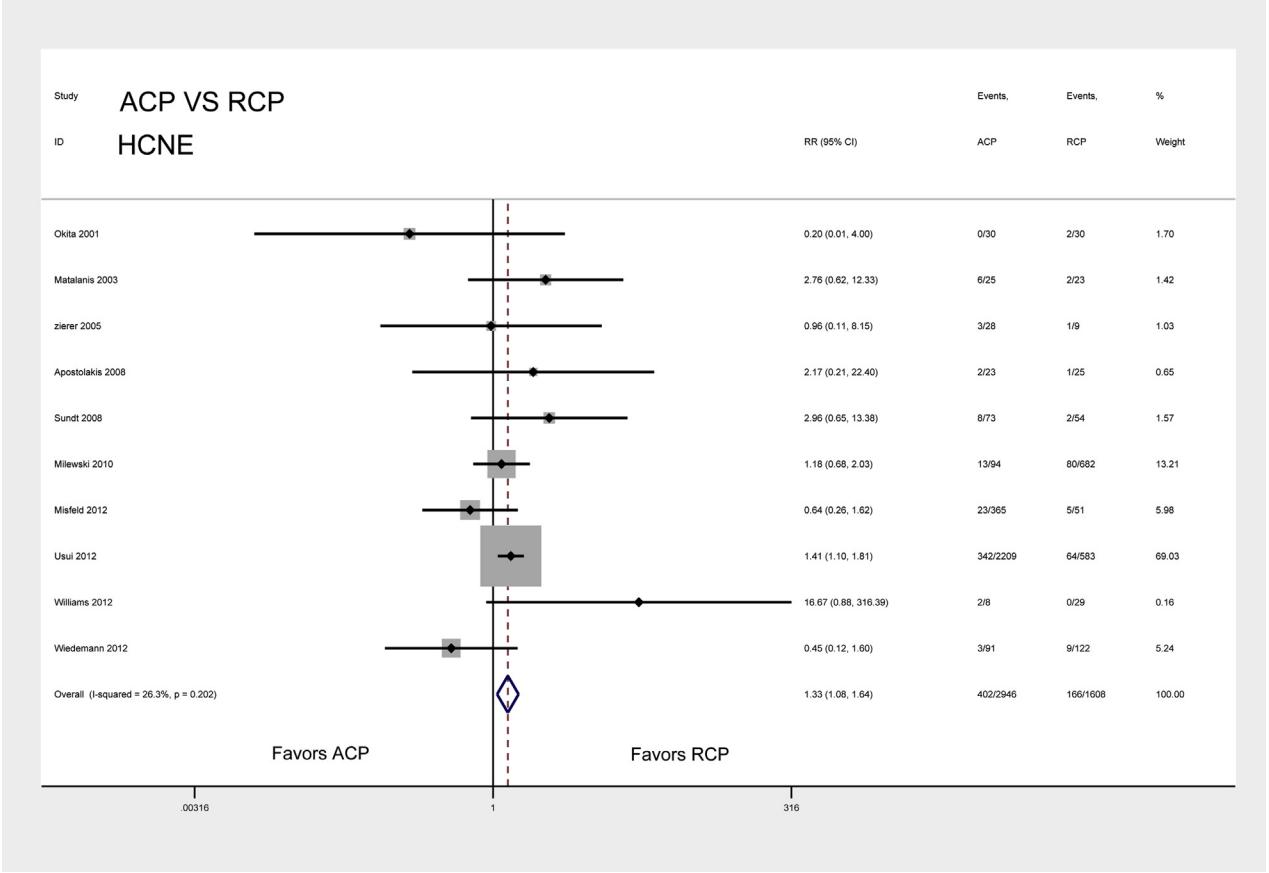

FIGURE 13. Sensitivity analysis of history of central neurologic events indicating that exclusion of study by Usui and colleagues[20] changes the total results most obviously. *ACP*, Antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *HCNE*, history of central neurologic events; *RR*, relative risk; *CI*, confidence interval.

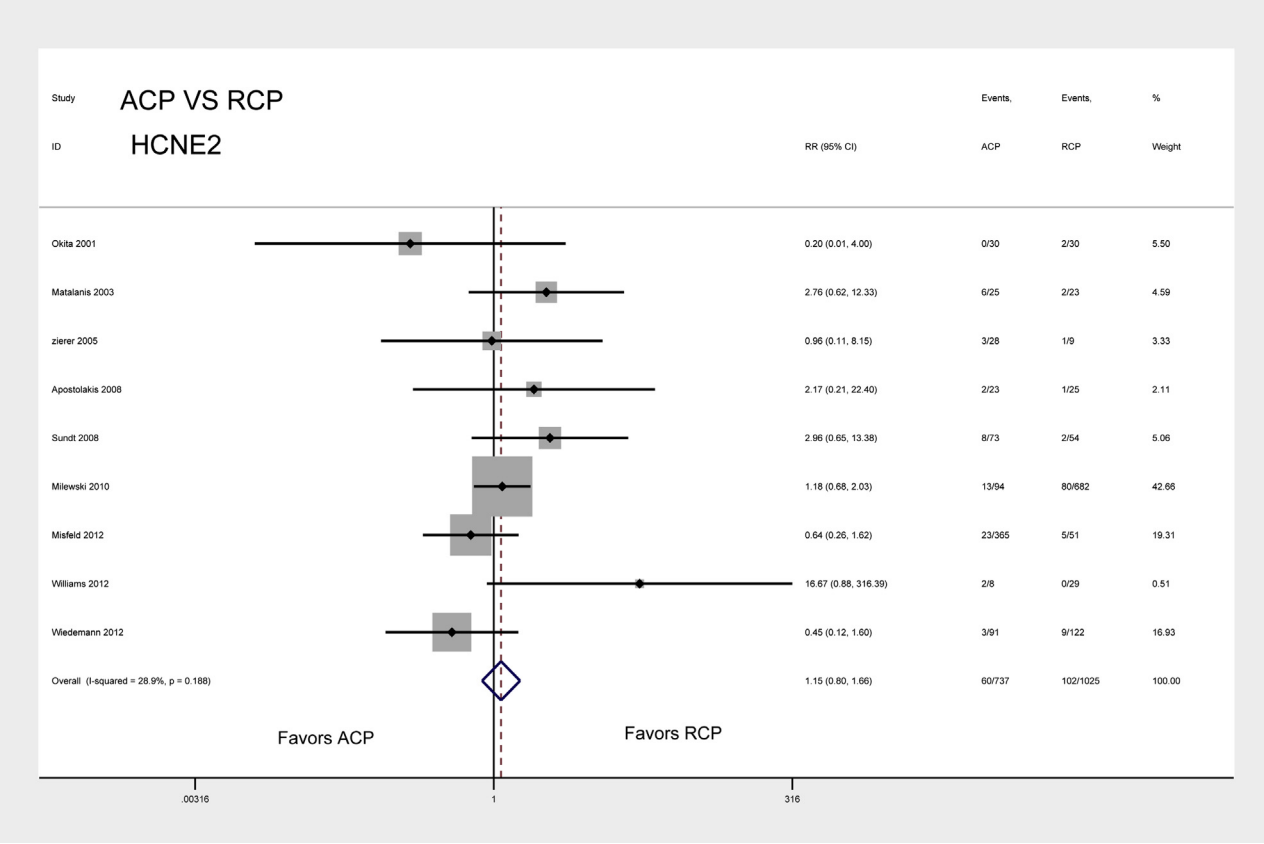

FIGURE 14. Comparison of antegrade cerebral perfusion (*ACP*) versus retrograde cerebral perfusion (*RCP*) for history of central neurologic events (*HCNE*) as 1 of the baseline data. *RR,* Relative risk; *CI,* confidence interval.

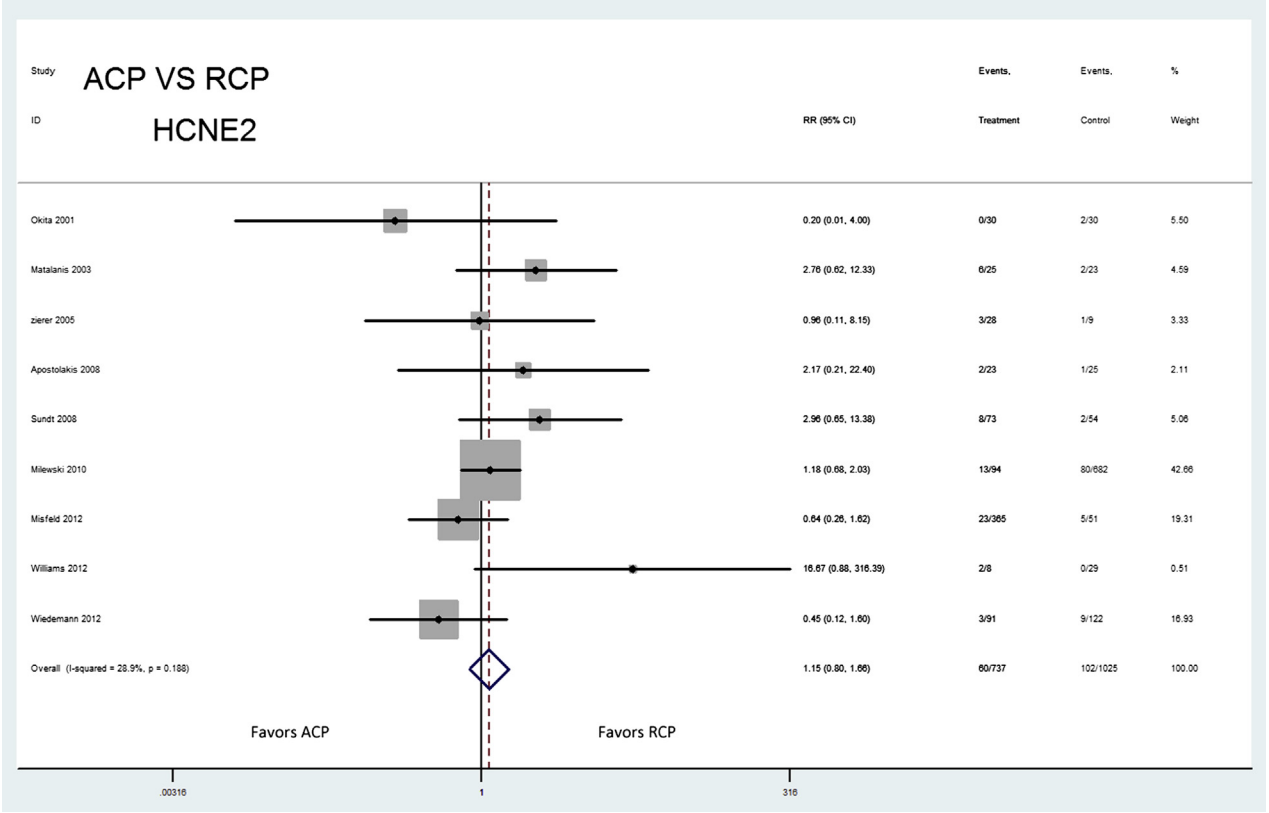

FIGURE 15. Comparison of antegrade cerebral perfusion (*ACP*) versus retrograde cerebral perfusion (*RCP*) for history of central neurologic events (*HCNE*) after the study by Usui and colleagues[20] was excluded. *RR,* Relative risk; *CI,* confidence interval.